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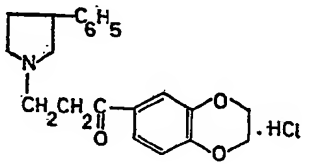
(54) PHARMACEUTICAL COMPOSITIONS CONTAINING AND PROCESS FOR PREPARING A BENZODIOPANE DERIVATIVE

(71) We, INSTITUT TOXIKOLOGII MINISTERSTVA ZDRAVOOKHRANENIA SSSR, an Institute organised and existing under the laws of the Union of the Soviet Socialist Republics, of ul. Bekhtereva 1, Leningrad, Union of the Soviet Socialist Republics, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

The present invention relates to a new drug of adreno-blocking action and a process for the production of the active principle of said drug, namely ω - (3^1 - phenyl - pyrrolidyl - 1^1) - 6 - propionylbenzo - 1,4 - dioxane hydrochloride.

According to the present invention a pharmaceutical composition (the active principle of which we have tentatively named Pyrroxan) comprises ω - (3^1 - phenyl - pyrrolidyl - 1^1) - 6 - propionylbenzo - 1,4 - dioxane hydrochloride of the formula



as active principle, and a pharmaceutically acceptable carrier therefor.

Pyrroxan is a strong adreno-blocking agent, having a blocking action predominantly on the alpha - adenoreceptors.

Pyrroxan is an effective drug in diseases and conditions arising from a pathological heightening of the sympathetic tone of the nervous system, principally the central nervous system. It also has a pronounced sedative effect and, moreover, completely suppresses the central action (tremor) of nicotine.

Pyrroxan is employed in diverse diseases and pathological conditions which is explained by its basic property, i.e. its adreno-blocking action, and its ability to normalize pathological stimulation of the posterior hypothalamus.

The principle indication for the use of Pyrroxan is for the abatement, prevention and treatment of diencephalic and hypertonic crises of sympathicotonic character. In such cases the therapeutic effect sets in within 30—40 minutes, and consequently the pharmaceutical composition can be used in emergency cases.

The pharmaceutical composition has a marked therapeutic effect in mixed diencephalic crises (diencephalitis with diencephalic epilepsy, hyperkinesis of potencephalitic nature, etc), proceeding with predominance of sympathetic tone.

Pyrroxan has a pronounced therapeutic effect in preparing patients with hypertension of hormonal origin for surgical intervention on account of tumours and when treating a hypertensive syndrome making difficult hormonotherapy of recurrences and metastases of breast cancer.

Pyrroxan is successfully used for aborting opium (morphine or codeine) abstinence symptoms. It is particularly effective in mitigating the most distressing symptoms (craving for the narcotic and insomnia) and facilitates the treatment of such patients in hospital. For aborting abstinence symptoms, Pyrroxan is administered in the ordinary dosage during the first week following the withdrawal of narcotics.

Pyrroxan is also indicated in the treatment of mental diseases proceeding with an anxiety-depression syndrome. In such cases Pyrroxan is used in the initial stage of treatment since it has a rapid therapeutic effect. This effect,

[Price 25p]

however, is often not lasting, which necessitates going over to the use of antidepressants.

On the basis of individual clinical observations the use of Pyrroxan in the ordinary dosage can be considered indicated in Mènière's syndrome and hyperstimulation of the vestibular apparatus of diverse aetiology (after the operation of fenestration, and in various forms of motion sickness—for example sea sickness and air sickness. In the latter conditions, Pyrroxan can be administered in conjunction with drugs of other pharmacological groups, specifically cholinolytic and antihistamine drugs.

On the healthy person, Pyrroxan has a slight sedative effect with no perceptible lowering of the normal blood pressure.

The pharmaceutical composition preferably contains the active principle in combination with a pharmaceutical filler for tablets or a solvent for injection solutions.

A 0.01 N aqueous solution of hydrochloric acid preferably is used as solvent for injection solutions. Solutions for injection preferably contain from 1 to 1.5 wt.% of the active principle.

Pyrroxan has been tested in clinics on 317 patients. The pharmaceutical composition was used for aborting, preventing and treating diencephalic and hypertonic crises of sympathicotonic character.

When the pharmaceutical composition was administered intramuscularly (15 to 30 mg of Pyrroxan) the patient's condition was mitigated in from 5 to 15 minutes and the crises was completely aborted in from 30 to 50 minutes: the blood pressure was normalized tachycardia and pain in the region of the heart and epigastrium ceased and symptoms of fright passed away.

Administration of Pyrroxan in mixed diencephalic crises (diencephalitis nature, etc) proceeding with a predomance of sympathetic tone, overcamediencephalic crises, normalized the blood pressure, and abolished seizures; patients felt considerably better subjectively, and sleep and appetite were normalized.

When the pharmaceutical composition was used in preparing hypertonic patients for surgical interventions on account of tumours and in treating a hypertensive syndrome making difficult hormonotherapy of recurrences and metastases of breast cancer a good therapeutic effect was achieved in from 2 to 4 days. A substantial hypotensive effect was observed, the patient's general condition improved and giddiness, headache and nausea disappeared. Pyrroxan was administered orally in doses of from 10 to 20 mg three times a day for a period of from 1 week to 1 month.

For aborting the opium abstinence syndrome, Pyrroxan was administered intramuscularly in a dose of 30 mg or orally in a dose of 60 mg. A therapeutic effect was noted in from 10 to 15 minutes when the pharmaceutical composition was injected and in from 30 to 40 minutes when given orally: vomiting, shivering and sneezing ceased, and coryza, lacrimation, muscular pain, a craving for the narcotic and insomnia disappeared.

A subjective feeding of satisfaction appeared and the back-ground of depression and the mood were normalized.

Pyrroxan was most effective in prolonged states of depression with a monotonous course. In pronounced melancholy Pyrroxan effectively abolished, for example, the feeling of dejection, heaviness in the chest and difficulty in breathing. In anxiety-depression states Pyrroxan temporarily abated anxiety.

The pharmaceutical composition preferably is administered orally in tablets or powders, or injected subcutaneously or intramuscularly in 0.01 N hydrochloric acid.

Recommended doses: orally from 0.015 to 0.032 g, from 1 to 4 times a day; injections, from 1 to 3 ml of 1% solution, from 1 to 3 times daily or from 1 to 2 ml of 1.5% solution once or twice daily.

In diencephalic and hypertonic crises the best effect is obtained with intramuscular administration of from 1 to 2 ml of 1.5% solution once or twice daily. A therapeutic effect is usually noted after a single injection.

In essential hypertension I and II stages, A and B, the pharmaceutical composition is prescribed orally for from 10 to 15 days in a dosage of from 0.01 to 0.015 g 3 or 4 times a day, or from 0.02 to 0.03 g 2 or 3 times a day, or subcutaneously or intramuscularly in doses of from 1—2 ml of from 1 to 1.5% solution.

In cases of abstinence symptoms (for example in withdrawal of opium, morphine or codeine) and in some forms of depression, Pyrroxan is prescribed intramuscularly in a dose of 30 mg or orally in single doses up to 60 mg, the daily dose being 90 or 180 mg respectively, while checking the arterial pressure for the first 3 to 6 days of treatment.

Treatment with Pyrroxan is possible in both in-patient and out-patient conditions.

It is advisable for the first administration of the pharmaceutical composition to be made under the observation of a physician and to begin with a single dose of 10 mg, gradually increasing the dose for 2 or 3 days until the most effective is reached, that is, from 30 to 40 mg orally or intramuscularly.

Maximum single doses for adults: orally, 60 mg; injection, 45 mg. Maximum daily doses: orally, 180 mg; injections, 90 mg.

The pharmaceutical composition has no side effects, and there are no absolute contraindications for its use. The use of Pyrroxan is not advisable in serious forms of atherosclerosis with pronounced stenocardia, in dis-

orders of the cerebral circulation and pronounced cardiac insufficiency.

The present invention also embraces a process for the production of the active principle of the foregoing drug, namely ω - (3¹ - phenylpyrrolidyl - 1¹) - 6 - propionylbenzo-1,4 - dioxan hydrochloride.

A process for the production of ω - (3¹ - phenylpyrrolidyl - 1¹) - 6 - propionylbenzo - 1,4 - dioxan hydrochloride is known which comprises reacting 3 - phenylpyrrolidine with 6 - acetylbenzo - 1,4 - dioxan and paraform in the presence of hydrogen chloride in alcoholic solution at the boiling point of the alcohol. The unreacted 6 - acetylbenzo - 1,4 - dioxan is then removed from the reaction mixture by extracting with ethyl ether. The reaction is made alkaline with potassium carbonate and the ω - (3¹ - phenyl - pyrrolidyl - 1¹) - 6 - propionylbenzo - 1,4 - dioxan base formed is extracted with ethyl ether, the ether extract acidified to acid reaction with an alcoholic solution of hydrogen chloride, and the precipitate of the final product is filtered out and crystallized from acetone. The yield is from 40 to 45%. The final product assays not less than 98%.

Disadvantages of said known process are the low yield of final product and the presence of impurities in the same which causes turbidity of aqueous solutions, making impossible its use in medical practice for paranteral administration.

It is an object of the present invention to obviate or mitigate the above-mentioned disadvantages.

According to the present invention there is provided a process for the production of ω - (3¹ - phenylpyrrolidyl - 1¹) - 6 - propionylbenzo - 1,4 - dioxan hydrochloride, comprising effecting reaction of 3 - phenylpyrrolidine, 6 - acetylbenzo - 1,4 - dioxan and paraform in a molar ratio of 1:1:2.6 in the presence of hydrogen chloride in alcoholic solution at a temperature within the range from 60 to 120°C; effecting removal of the unreacted 6 - acetylbenzo - 1,4 - dioxan; rendering alkaline the reaction mixture thus obtained; recrystallizing from ether the ω - (3¹ - phenylpyrrolidyl - 1¹) - 6 - propionylbenzo - 1,4 - dioxan base formed; and effecting reaction of the recrystallised base with hydrogen chloride by recrystallization from ethanol acidified with the hydrogen chloride.

A preferred embodiment of the present process is carried out as disclosed hereinbelow.

3 - Phenylpyrrolidine is dissolved in alcohol and acidified with an alcoholic solution of hydrogen chloride. 6 - Acetylbenzo-1,4 - dioxan and paraform are added and the mixture boiled at a temperature within the range from 60 to 120°C. The alcohol is distilled off and the residue diluted with water. The unreacted 6 - acetylbenzo - 1,4 - dioxan is then extracted from the reaction mixture with ethyl ether and regenerated. The reaction mixture is made alkaline and the ω - (3¹ - phenylpyrrolidyl - 1¹) - 6 - propionylbenzo - 1,4 - dioxan base formed is extracted with ether, the ether extract dried over calcined magnesium or sodium sulphate, the solvent distilled off and the residue recrystallized from ethyl ether. A crystalline product is obtained; m.p. 64—66°C. The base is dissolved in acetone and to the solution there is added with stirring and cooling to 0 to +5°C an alcoholic solution of hydrogen chloride to pH 5. The precipitate of the final product which forms is filtered off, dried at a temperature within the range from 50 to 60°C and recrystallized from ethanol acidified with hydrogen chloride. The yield of final product is 50—60%. The final product assays not less than 99%; m.p. 137—142°C (within a range of 2°C).

The present process yields a final product of higher quality than the previously known process (the product obtained by the present process assays not less than 99%, while the product obtained by the known process assays not less than 98%). Moreover the yield of final product is increased.

The process of the present invention is illustrated in the following Example.

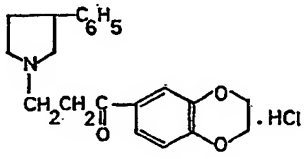
EXAMPLE

15.5 g (0.105 g-mol) of 3 - phenyl - pyrrolidine is dissolved in 60 ml of absolute ethyl alcohol and acidified to acid reaction (pH 3) with 25% alcoholic hydrogen chloride. 18.4 g (0.105 g-mol) of 6 - acetylbenzo - 1,4 - dioxan and 8 g (0.27 g-mol) of paraform are added and the mixture refluxed at 78—80°C for 6 hrs. The alcohol is distilled off and the residue poured from the flask into 500 ml of water. The unreacted 6 - acetylbenzo - 1,4 - dioxan is extracted from the water layer with ether (3 times with 50 ml portions) and regenerated. The aqueous layer is made alkaline with 50 ml of 10% sodium hydroxide and the base formed is extracted with three 75 ml portions of ether. The combined ethereal extracts are dried over calcined magnesium sulphate, the solvent distilled off and the residue is recrystallized from ether. 21.2 g of base are obtained in the form of a white or slightly cream-coloured crystalline substance. 21.2 g of the base are dissolved in 150 ml of acetone, the solution is filtered, and 25% alcoholic hydrogen chloride is added with stirring and cooling to 0 to +5°C to pH 5. After stirring for 1 hr the precipitate is filtered off, washed with acetone, dried at 60°C and recrystallized from 75 ml of ethanol acidified with 0.5 ml of 25% alcoholic hydrogen chloride. These are obtained 19 g (51% yield) of ω - (3¹ - phenylpyrrolidyl - 1¹) - 6 - propionylbenzo - 1,4 - dioxan hydrochloride in the form of a

white or slightly yellow crystalline substance; m.p. 139—141°C.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition of adrenoblocking action, comprising ω - (3^1 - phenyl - pyrrolidyl - 1^1) - 6 - propionylbenzo - 1,4 - dioxan hydrochloride of the formula



as active principle, and a pharmaceutically acceptable carrier therefor.

2. A pharmaceutical composition as claimed in claim 1, in the form of tablets, or as a solution in a solvent for injection.

3. A pharmaceutical composition as claimed in claim 2, wherein the solvent is 0.01 N aqueous hydrochloric acid.

4. A pharmaceutical composition as claimed in claim 3, wherein the solution contains from 1 to 1.5 wt.% of the active principle.

5. A pharmaceutical composition of adrenoblocking action as claimed in claim 1, and substantially as herein before described.

6. A process for the production of ω - (3^1 - phenylpyrrolidyl - 1^1) - 6 - propionyl - benzo - 1,4 - dioxan hydrochloride, comprising effecting reaction of 3 - phenylpyrrolidine, 6 - acetyl - benzo - 1,4 - dioxan and paraform in a molar ratio of 1:1:2.6 in the presence of hydrogen chloride in alcoholic solution at a temperature within the range from 60 to 120°C; effecting removal of the unreacted 6 - acetylbenzo - 1,4 - dioxan; rendering alkaline the reaction mixture thus obtained; recrystallising from ether the ω - (3^1 - phenylpyrrolidyl - 1^1) - 6 - propionyl - benzo - 1,4 - dioxan base formed; and effecting reaction of the recrystallised base with hydrogen chloride by recrystallisation from ethanol acidified with the hydrogen chloride.

7. A process as claimed in claim 6 substantially as hereinbefore described.

8. A process for the production of ω - (3^1 - phenylpyrrolidyl - 1^1) - 6 - propionyl - benzo - 1,4 - dioxan hydrochloride, according to the Example.

9. ω - (3^1 - phenylpyrrolidyl - 1^1) - 6 - propionylbenzo - 1,4 - dioxan hydrochloride, whenever produced by the process according to any one of claims 6, 7 and 8.

10. A pharmaceutical composition comprising ω - (3^1 - phenylpyrrolidyl - 1^1) - 6 - propionylbenzo - 1,4 - dioxan hydrochloride as claimed in claim 9, and a pharmaceutically acceptable carrier therefor.

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